Statistical Studies in Immunity.
The Incubation Period and the Crisis.

BY

JOHN BROWNLEE, M.A., M.D.,

Physician Superintendent, City of Glasgow Fever and Smallpox Hospitals, Belvidere.

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Statistical Studies in Immunity. The Incubation Period and the Crisis. By JOHN BROWNLEE, M.A., M.D., Glasgow, Physician Superintendent, City of Glasgow Fever and Small-pox Hospitals, Belvidere.

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IN the present paper it is intended to discuss a few of the facts concerning incubation periods and the days of crisis in different diseases in relation to questions of immunity. Unfortunately data referring to large numbers of cases are not readily obtainable even in the records of a large infectious diseases hospital. In some diseases such as typhus fever the most recent text-books give practically no incubation data, and even in Glasgow where this disease is still present to a small extent, and where therefore the conditions to determine the facts are most favourable, the number of instances in which the incubation period can be fixed from a single contact is so small as to make the figures useless for statistical purposes. Other diseases such as Measles are very infectious for a certain number of days before definite diagnosis is possible, and in this case the number of instances in which the incubation period can be fixed within 24 hours is surprisingly small. Two diseases alone, namely varicella and variola, have been found to furnish good data for the present purpose. Of the former I have been able to collect the incubation periods of sixty-five cases, and of the latter forty-six. In the case of the former I have seen no evidence that patients incubating it possess any infectivity prior to the appearance of the symptoms. Twice it has happened that children have been transferred from wards on the day prior to the appearance of a varicellar eruption without the subsequent development of the disease in the wards from which they were removed. The characteristic rash in most cases is the earliest symptom. In consequence as a considerable number of children suffering from other diseases are admitted to the hospital incubating this disease, unknowingly placed among susceptible persons, and removed on the first appearance of the new illness, all the conditions necessary for the accurate determination of the incubation period are present. Variola also affords a considerable amount of data. In the recent epidemics in Glasgow in all forty-six persons were ascertained to have visited persons suffering from the disease on a single occasion, and so far as could be discovered to have been exposed to no other source of infection. Many of these developed the disease in districts of the city in which no other cases were known to exist, thus fulfilling the necessary criteria.

In Scarlet Fever and German Measles a certain number of incubation periods have also been ascertained in the hospital. For further details the Report of the Clinical Society of London on this subject has been consulted, but the chief additional data used have been those recorded by Dr. Dukes, Physician to the Rugby School.[1] These have been ascertained under the same conditions as my own figures, are liable to the same sources of error, and when considered separately show a general concordance.

One other source for the study of incubation periods in large numbers has been afforded in recent years by the serum treatment of diphtheria, and in this case a large body of statistics of considerable interest has been accumulated.

For the determination of a number of points, the data concerning varicella and variola are the most complete. For varicella the accompanying table shows the number of cases which have developed on each day after exposure to infection, and it is seen that the shortest time at which chicken-pox has developed in the hospital cases is eleven days after infection, and nine days in those of Dr. Dukes, while the greatest number sicken fifteen days after exposure. After the twenty-four days no case has been observed to occur. It is to be noted that the progression from a few cases developing eleven days after exposure to the maximum and thence to the decline to zero is fairly continuous, but the numbers occurring after the incubation period of 11, 13, 15, and 17 days are much larger than those after 10, 12, 14, and 16 days, a fact perhaps to be explained by the existence of some such condition as a two day stage in the life history of the organism. The numbers are however too small to make this inference certain. A further point of importance is observed when the different groups of cases occurring in each separate infection is considered. It

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[1] *Lancet*, 1881, October 29th, p. 743, and 1899, April 29th, p. 1147.

TABLE I.—Table showing the incubation periods of cases of Varicella, Variola, German Measles and Mumps in groups where a number of persons were infected after exposure on a definite date, and collectively where only one secondary case occurred. Those marked D are recorded by Dr Dukes.

NUMBER OF CASES DEVELOPING AFTER . . . DAYS OF EXPOSURE.

Name of Disease.	No. of Group.	Days after Exposure.																	Total.
		8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
VARICELLA or CHICKENPOX.	1	...	...	...	2	1	...	1	...	...	...	...	...	...	...	...	...	...	...
	2	...	...	...	...	2	2	...	...	...	...	...	...	...	...	...	...	...	...
	3	...	...	...	...	...	2	...	1	..	...	...	...	...	...	...	...	...	...
	4	...	...	...	...	...	1	2	...	...	...	...	...	...	...	...	...	...	...
	5	...	...	...	...	...	...	1	2	1	...	...	...	...	...	...	...	...	...
	6	...	...	...	...	...	...	1	...	...	1	...	...	...	...	...	...	...	...
	7	...	...	...	..	...	...	1	4	...	2	...	...	...	...	...	...	...	...
	8	...	...	...	...	...	...	...	3	...	...	...	...	...	...	...	...	...	...
	9	...	...	...	...	...	...	...	1	...	...	2	...	...	...	...	...	...	...
	10	...	...	...	...	...	...	...	2	...	1	...	...	...	...	...	...	...	...
	11	...	...	...	...	...	...	...	...	5	.	...	...	...	...	...	...	...	...
	12	...	...	...	...	...	...	...	...	...	5	...	...	...	...	...	...	...	...
	13	...	...	...	...	...	...	...	...	...	2	...	...	...	...	...	...	...	...
	14	...	...	...	...	...	...	...	...	...	...	.	1	...	...	1	..	...	...
	15	...	...	...	...	...	...	...	...	...	...	...	...	...	...	2	...	1	...
	Others	...	...	...	1	...	2	1	..	1	...	2	1	2	1	1	..	...	...
	,, D	...	1	...	..	...	3	2	8	3	3	2	3	...	...	...	...	...	...
	Total,	..	1	...	3	3	10	9	21	10	14	6	5	2	1	4	...	1	90
VARIOLA or SMALLPOX.	1	1	..	3	1	...	...	...	...	...	..	...	...	...	...	...	...	...	...
	2	...	2	1	1	...	...	...	...	...	...	...	...	...	...	...	...	...	...
	3	...	...	...	...	4	..	...	...	...	...	...	...	...	...	...	...	...	...
	Others	2	2	4	8	4	5	6	1	1	...	...	...	...	...	..	...	..	...
	Total,	3	4	8	10	8	5	6	1	1	...	...	...	...	...	...	...	.	46
RÖTHELN or GERMAN MEASLES.	1	...	...	...	..	1	...	1	...	...	...	...	...	..	...	...	...	...	..
	2D	...	...	..	...	1	...	2	...	...	...	..	...	...	...	...	...	...	...
	3	...	...	...	...	...	...	2	...	...	...	...	...	.	...	...	...	..	...
	4	..	...	...	...	...	...	1	...	1	..	...	..	...	...	..	...	...	...
	5D	...	...	...	...	...	...	...	1	...	...	1	...	...	...	...	...	...	...
	6	...	...	...	...	...	...	...	...	2	...	..	...	...	..	...	...	..	...
	7D	...	..	...	...	...	...	...	...	3	...	..	.	.	...	...	...	...	...
	8D	...	...	...	...	...	...	...	...	2	2	..	...	...	..	...	...	...	...
	9D	...	..	...	...	...	...	...	...	1	...	1	...	...	.	...	...	...	...
	10	...	...	...	...	...	...	...	...	..	..	3	3	1	...	...	...	...	...
	11	...	...	...	...	...	...	...	...	...	...	..	3	1	...	...	...	...	...
	Others	...	...	..	..	1	1	4	1	2	1	...	...	1	...	...	...	...	...
	Total,	...	...	..	...	3	1	10	2	11	3	5	6	3	...	...	...	...	44
PAROTILIS or MUMPS. DR DUKES.	1	..	...	...	...	...	...	1	...	1	...	..	1	...	...	...	..	...	...
	2	...	...	...	...	..	..	...	..	1	...	...	1	...	..	...	...	1	...
	3	...	...	...	...	...	...	...	...	...	3	...	...	1	...	...	...	..	...
	4	...	...	...	..	...	...	...	...	..	1	..	1	.	...	..	...	...	...
	5	...	...	...	...	...	...	...	...	...	2	3	..	2	...	...	..	...	...
	6	...	...	...	...	...	...	..	...	...	...	2	.	..	...	...	.	...	...
	7	...	...	...	...	...	.	..	...	...	..	1	1	...	.	...	...	.	...
	8	...	..	...	...	...	...	...	1	...	...	..	4	1	...	...	..	...	...
	9	..	...	...	...	...	...	.	...	...	...	...	3	1	...	...	...	...	...
	10	...	...	...	...	...	1	...	...	...	1	...	...	2	4	...	...	.	...
	11	...	...	...	...	...	...	..	..	...	...	...	...	...	1	1	...	...	...
	Others	...	...	...	...	...	..	..	1	1	4	4	6	1	1	1	1	1	...
	Total,	...	...	.	...	...	1	1	2	3	11	10	17	8	6	2	1	2	64

will be seen by a reference to Table I. that when a number of persons are infected from the same source at the same time there is very little variation in the incubation period. Each group of infected persons is tabulated so as to show the numbers who sickened on each day after exposure. In no group does the length of incubation vary more than three complete days, although the incubation period of all cases of chicken-pox has a range of fourteen days. In other words the incubation period in any definite infection depends far more on the individual peculiarities of the germ infecting than on the constitutional peculiarities of the person infected. This is a very important point, and is in direct accordance with what we know of many properties of different races of the same organism when examined *in vitro.*

With smallpox in the same way may be seen in Table I the general manner in which the incubation varies from the period of infection till the onset of the initial sickness. The range is not nearly so great as in chicken-pox, nor is there any evidence of the existence of a bi-daily period in the life history of the organism.

In this disease only three groups of infection disseminated at the same instant among a variety of persons, have come under notice. In two of these a child with a confluent eruption of smallpox was taken to a public dispensary, and in the third a whole family was exposed to infection on a definite date with the result that five members sickened. Again it is to be observed (Table I.) that the date of sickening in these cases varies much less than the total range of incubation. The limit of variation is the same as that for chicken-pox, namely three complete days.

In Table I. the incubation periods of mumps, scarlet fever, and German measles are also given. In all these instances it is to be noted that the range of duration of the incubation period differs little in each group compared with the total range. The greatest diversity is seen in the case of mumps, but even in this, only in three instances out of eleven does it exceed a very few days. It is apparently, so far as can be ascertained by the tables at our disposal, a fact that in general some quality of the infecting organism is the main cause of the length of the incubation period. It is to be noted that the figures for German measles or rötheln also gives some indication of a two-day period in the life history of the infecting organism.

The influence of the age of the patients on the incubation period does not seem to be very great. Dr. Dukes, in his papers already referred to, has expressed this opinion, and in the accompanying table (Table II. A) it will be seen that this conclusion is also true for most cases of chicken-pox, while in the case of smallpox (Table II. B) it is found that the average incubation period for those patients suffering from smallpox above twenty-five years of age is within a fraction of a day the same as the average for those below twenty five. No distinction between the patients as regards age has therefore been deemed necessary in this discussion.

TABLE I. A.—THE SAME FOR SCARLATINA.

No. of Days.

	-1	1	2	3	4	5	6	7	8	9	10
1 D	...	2	...	...	...	...	...	...	...	...	...
2 D	...	1	1	...	...	...	...	...	...	...	...
3 D	...	...	...	3	...	...	...	...	...	...	...
4	...	...	...	1	1	1	...	...	...	...	...
5 D	...	..	...	...	2	...	.	...	...	...	...
Others D	1	1	1	1	...	2	1	...	1	...	...
Others Dr. Murchison	1	...	1	1	...	...	...	...	...	...	...
Others	...	1	1	1	...	...	...	...	...	...	1 ?
Total	2	5	4	7	3	3	1	...	1	...	1 ?

TABLE II. A.

Incubation Period of Chicken-pox Relative to Age.

Years of Age.	No. of Cases.	Mean Incubation Period in Days.
-1	3	16·6
1-2	10	16·4
2-3	6	18·3
3-4	18	15·7
4-5	10	16·0
5-6	5	13·6
6-7	7	15·7
7-8	1	15 0
8-9	3	14·1
9-	2	15·5

In regard to the length of the incubation period being dependent

TABLE II. C.

TABLE II. B.

Incubation Periods in Cases of Smallpox

Number of Days from Infection.	CHARACTER OF CASE IN				AGE OF PATIENTS IN			
	Vaccinated.			Unvaccinated.	Vaccinated.		Unvaccinated.	
	Confluent.	Abundant.	Sparse.	Confluent.	< 25 Years.	> 25 Years.	< 25 Years.	> 25 Years.
8	...	1	2	...	...	3	...	...
9	...	...	4	...	3	1	...	...
10	2	3	4	...	4	4	...	...
11	...	3	7	...	4	6	...	..
12	2	1	5	...	3	5	...	...
13	...	2	3	...	3	2	...	...
14	...	1	4	1	...	5	1	...
15	...	1	...	...	...	1	...	...
16	...	...	1	...	...	1	...	...
17	...	...	...	...	...	...	...	...
Mean	11	11.5	11·3	14	11	11·7	14	...

on the infecting organism, it is important to know if this is a permanent quality of a particular race of an organism or a quality which may vary in succeeding generations of the same organism. All the cases bearing on this which I have been able to collect are given in the accompanying table (Table III.), and it is apparent that while the period of incubation of successive groups of cases infected by the same organism is fairly constant, yet the correspondence is not so absolute as to warrant the conclusion that the incubation period, which in each individual case is dependent on the state of the organism at the moment, remains in a sequence of the infections also constant in a like manner. In other words, the length of the incubation period is not a property which is inherited in an absolute manner. Out of the twelve cases given in the table the incubation period is hereditary in ten, but in the other two considerably different, or at least different to an extent beyond the limits of the three complete days which were found to hold in the cases previously considered.

Another important point is the relation of the incubation period to the severity of the attack, Unfortunately here again is a very great difficulty in obtaining evidence. With regard to chickenpox differences of severity can hardly be recorded, while with regard to smallpox the modifying effect of vaccination must be taken into account. With the small number of cases at our disposal the latter is impossible. When the cases are tabulated according to degrees of severity of attack, no difference is observed between the mean incubation periods of the different groups, an observation somewhat contrary to the usual belief, but this will receive some confirmation in a later part of this paper. In the actual groups, where several persons were infected at the same time, there is likewise no evidence that there is any association between incubation period and severity, and in the instance where four persons sickened on the same day after exposure, in two of these the eruption was sparse, in one abundant, and in the fourth confluent, although the patients presented no great difference either in their age or in the character of their vaccination (Table II. c).

It must be evident from what has been said that unless incubation periods are collected over a considerable space of time and in different epidemics, or unless these statistics of different epidemics are compared only among themselves little trust can be placed on the statement that severe cases are in general associated with short incubation periods. As has been seen the particular

TABLE III.—Table showing the duration of the incubation period in second infections by the same organism. In the Chicken-pox cases the infection in the second group is counted as from the first case in the first group.

Disease.	Group	Days after exposure at which disease developed. First generation.											Days after exposure at which disease developed. Second generation.											
		12	13	14	15	16	17	18	19	20	21	22	12	13	14	15	16	17	18	19	20	21	22	
CHICKEN-POX.	1	...	...	1	3	1	...	...	...	...	...	...	...	...	...	...	...	1	1	1	...	...	...	x
	2	..	...	...	...	...	...	...	1	...	...	1	...	...	...	...	...	...	2	...	...	1	...	x
	3	...	...	1	...	...	...	1	...	...	...	..	...	...	...	...	1	...	...	...	1	1	...	x
	4	...	...	...	...	...	1	...	...	...	...	...	...	...	...	...	...	5	...	...	...	...	...	x
	5	...	...	...	2	...	1	...	...	...	...	...	4	2	3	2	...	...	...	...	...	...	...	o
	6	...	...	...	...	...	1	...	...	...	...	...	...	...	...	1	1	2	...	...	...	...	...	x
	D7	...	...	...	1	...	...	...	...	...	...	...	...	...	...	2	(14-16 days)		...	...	...	...	...	x
RÖTHELN.	D1	...	...	1	...	...	...	...	...	...	...	...	...	...	...	...	3	...	...	...	...	...	...	x
MUMPS.	D1	...	...	...	...	...	...	1	...	..	...	...	...	...	...	...	...	...	1	1	...	...	...	x

Disease.	Group.	1	2	3	4	5	6	7			1	2	3	4	5	6	7	
SCARLET FEVER.	D1	...	...	...	1	...	...	...			...	.	...	...	2	...	...	x
	D2	...	...	...	...	1	...	...			...	1	1	...	8	...	...	o
	D3	...	...	...	1	...	...	...			...	2	...	...	...	...	...	x

x Those marked thus are in favour of the inheritance of the incubation period by the germ.

o Those marked thus show divergence from this property.

organism has the chief part in determining the incubation period. With regard to smallpox, Zülzer is constantly quoted to the effect that hæmorrhagic smallpox has a shorter incubation period than other cases. Counting to the appearance of the eruption this is possibly true, but counting to the onset of symptoms, as has been done in my figures, the evidence is not complete, I have not seen Zülzer's original paper, but the synopsis in Virchow's Jahrbuch does not suggest that the evidence is conclusive.

One consideration demands mention here. The whole body of phenomena associated with the incubation period just detailed will be found a little later to have a very marked analogy with the phenomena displayed by the duration of the disease in the infected organism. The same kind of distribution is noted, and it strongly suggests that the incubation period represents to some extent a disease of the attacking organism which it must survive before itself is capable of producing disease in its host; in other words, it must manufacture anti-bodies for its own protection before it can proliferate to a sufficient extent to cause an attack of disease.

A second group of cases of incubation periods now falls to be considered. In this the cause of the illness, in place of being the toxin produced by an infecting agent, appears to be a secondary substance produced after a foreign body not toxic in itself has been introduced into the system, by the development of an anti-body which either forms a toxic combination with the original substance or produces a break down of this into toxic substances. The disease in this case is then an accident due to the organism utilising its ordinary methods of defence against substances for which the process has not originally been designed.

Such a condition is produced when horse serum is injected in the treatment of diphtheria. In this case we have absolute data based on numbers of cases much in excess of what are procurable in the case of the ordinary infectious diseases, and also much more correct, for both the date on which the foreign substance is administered and the amount are definitely known. In close connection with this class of poisons are those associated with some of the complications of the specific fevers which are evidently due to substances altered in much the same way either by combination or break down. Chief among such are the arthritis and nephritis of scarlet fever. In this class also the paralysis following diphtheria is probably also to be included.

The exact incubation period, however, is not so definite in these instances, as the substance subsequently made toxic is produced at a period of the disease of which we are ignorant, and the onset of the fever must in consequence be taken as the date from which the incubation has to be calculated.

Certain theoretical difficulties present themselves at this point. While it is moderately obvious that the serum fever must be due to an alteration in some substance contained in the serum, which is itself not poisonous, it is not at all clear whether the altered substance is one which demands the elaboration of a new series of anti-bodies before it can finally be eliminated, or whether the same agents already formed which have begun the destruction of the non-toxic substance are themselves sufficient to complete its destruction. In the former case there will be an almost complete analogy between the serum fever and an ordinary specific fever, though the serum fever is really an auto-intoxication, while in the latter there is sufficient difference to demand caution in the application of results obtained from a consideration of serum fever, to the other forms of disease. With all the drawbacks the large numbers available makes the statistics of very considerable value. The cases on which the figures are based consist practically wholly of children, and in consequence the material presented is moderately homogeneous. Again, Table IV. shows that if the dose of serum be higher than 6000 units neither size of dose nor type of case makes any difference in the frequency with which the rashes occur. In this table all cases which lived for nine days before death in whom no rash developed prior to that date are included among the negative figures. Such cases were very few, most deaths occurring within nine days of admission to hospital. This undoubtedly makes a slight difficulty in estimating exactly the effect which the severity has upon the likelihood of the rash developing, but the figures on which the results are based are otherwise so homogeneous that it does not seem necessary to make any special inquiries into the effect of this. These facts are to some extent different from what have been recorded by other observers, both in the frequency with which rashes occur and in the absence of effect on their frequency produced by the character of the case. But these matters must be subject to a good deal of variation in different places due to difference of race.

In Table V. the total rashes are classified in the numbers in which they occurred on each day after inoculation. Where two

TABLE IV.—Showing the frequency of rash after serum administration according as the cases are divided in relation to the amount of antitoxin administered and also as regards the severity of the attack of diphtheria.

AMOUNT OF ANTITOXIN IN UNITS.

	3000-6000	-9000	-12,000	18,000	-30,000	30,000-	Total.
Numbers with Rash	2	29	64	89	52	12	248
Do. without Rash	8	26	58	75	42	6	215
Relation to Severity[1]	**Mild.**	**Mod.**	**Severe.**	**Very Severe.**	**Intra-venous.**	**Other Diseases**	**Total.**
Numbers with Rash	69	63	77	39	28	11	259
Do. without Rash	56	58	61	40	17	17	232

[1] The intravenous numbers are included also in the severe and the very severe. The other diseases are not included in the first table, as most received very small doses of serum.

TABLE V.—Table showing the Incubation Period of Serum Rashes following the injection of Serum in Diphtheria and Plague.

	DIPHTHERIA.			
Day of Appearance.	Total Rashes.	Urticarial Alone.	Intra Venous Injection.	PLAGUE.
3	1	1	...	...
4	6	3	2	1
5	11	8	2	3
6	14	6	3	1
7	26	21	4	6
8	35	28	4	6
9	57	45	7	1
10	41	36	2	2
11	18	14	...	1
12	8	6	.	...
13	15	11	2	...
14	5	5	2	...
15	9	3	...	...
16	6	3	...	...
17	3	1	...	...
18	1	...	...	...
19	2	2	..	...
20	...	...	..	...
21	..	...	...	...
22	1	...	..	...
Total of	259	193	28	21
Mean Day Appearance.	9·50	9·50	8·32	7·38

doses of serum have been given the first has been chosen as the date from which to calculate. This table shows that the commonest day for the rash to appear is the ninth after inoculation.

Serum has been given in two ways; in the great majority of the cases subcutaneously, but in a smaller number of cases, twenty-eight in all, directly into a vein. The general behaviour of the succeeding phenomena is so much the same as to make it unnecessary to discuss them separately, except to state that the mean date of appearance is 1.2 days earlier than that when the administration was subcutaneous. Whether the rash appears definitely, as has been seen in the case of the specific fevers, with an incubation period appropriate to each separate specimen of serum obtained from each different horse, cannot be ascertained from the records of the hospital, as the different consignments have not been noted separately, but it is possible that the same phenomena holds here as well. The serum used for the protection of the persons who had been exposed to the infection of plague is prepared, like that of diphtheria, by immunizing horses, and produced exactly similar symptoms. In this case it all consisted of one consignment. The figures are tabulated for comparison, and it is seen that of twenty-one cases in which the rash followed the injection of the serum the mean day of occurrence was 7.4 days, or fully two days earlier than the mean of the days of appearance of the serum rash in diphtheria; while the total range of variation of date was only seven days, as against twenty in the latter case. Were the serum of each horse collected separately it is probable that it would be found that the range of appearance of the subsequent rash were even more definitely limited.[1]

The data for determining the relation between the severity of the rash and the incubation period are, in the case of serum sickness, very numerous, but unfortunately there are special difficulties in the application. These arise because the intoxication produced by the serum is unfortunately apparently not due to a single poisonous substance but to a complex of poisonous substances, each of which produces a class of symptoms proper to itself. The most common rashes are the urticarial and the morbilliform. The two are frequently seen in the same patient, with a few days' interval between them, the urticarial in general occurring first. Some other forms, such as that of erythema circinatum with fever, are comparatively rare, nearly always occur late, and are definite clinical entities. In addition, true relapses of the rashes seem sometimes to occur, and are difficult to explain on any theory. One such occurred recently, when the patient suffered from an urticarial rash at the usual interval after inoculation, and again, after the space of six weeks, had a return of the same eruption, although personally she had not so far as she knew ever had an attack of urticaria before.

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[1] Since the above was written an example has been noted. Twenty-one children received on the same day a protective inoculation of antidiphtheritic serum all from the same consignment. Of these five developed no rash. In seven the rash appeared on the seventh day after inoculation, in four on the eighth day, in three on the ninth, and in two on the tenth day, showing a small range of distribution of the dates of appearance of rash, and indicating that here also the incubation period depended more on the injected material than on the patient treated.

The duration of the rash has been taken out in two ways; first, the total duration of all forms of rash, with the day of first appearance; and, secondly, the same facts for the urticarial form alone. A reference to the table (Table VI.) will show that in the former case the mean duration of the rash where the

TABLE VI.—Table showing the number of cases with each length of Incubation Period and the duration of rash.

Duration of Rashes in Days.	ALL CASES. Incubation Period.			URTICARIAL RASHES ALONE. Incubation Period.		
	3-7 Days.	8-10 Days.	11 Days and upwards.	3-7 Days.	8-10 Days.	11 Days and upwards.
1	7	9	8	8	13	10
2	12	46	24	9	33	14
3	18	37	21	11	32	12
4	9	26	9	7	19	..
5	4	7	3	1	8	7
6	3	3	4	1	2	1
7	1	2	1	1	...	1
8	2	1	...	1	1	...
9	...	...	..	...	...	...
10	...	1	...	..	1	...
11	1	...	...	...	...	...
12	...	..	...	...	...	...
13	...	..	...	...	...	..
14	...	1	...	...	...	...
15	...	...	...	...	...	...
16	...	..	...	...	...	...
17	1	...	...	..	...	...
18	...	...	...	...	...	...
19	...	..	...	...	...	...
Mean duration of Rash.	3·64	3·12	2·9	2·9	2·9	2·7

incubation period was under seven days was 3.64 days, where the incubation period was 7-9 days 3.12, and above that 2.9; but if the urticarias alone be considered the corresponding figures are 2.9, 2.9, and 2.7. The former figures show some difference, but the latter very little, and in the light of the complexity found in illnesses due to serum, and of the fact that the long-continued morbilliform rash is one with a shorter range of incubative period, it cannot be said that there is any very definite evidence that a short incubation period is associated with a severe disease.

P2

We now come to the consideration of the facts relating to the crisis in disease. Apparently a period arrives when the attacked organism is able to manufacture anti-bodies in sufficient amount to neutralise the poisons of the disease quickly and effectively. In the diseases in which this phenomenon appears it occurs without any essential difference, except that its duration varies a little; it is shortest in relapsing fever, rather longer in pneumonia, and may extend to as much as three days in typhus fever; but in all it is associated with moistening of the tongue and sweating, clearing of the brain, and increased urinary discharge. It is to be noted in the first place that, as seen in the adjoining table (Table VII.), the distribution of the dates of recovery has marked similarity to those of incubation, whether diseases ending by crisis or lysis are chosen.

The significance of the date of recovery in interpreting the phenomenon of immunity is very considerable. It provides a means of comparing the method in which anti-bodies are produced in persons of different susceptibility and of different ages, and of gaining some information as to the reasons why decreased resistance may be associated with decreased susceptibility to the disease. It will be found by an examination of the tables presented,—compiled by different observers,—that from youth to age in the diseases which end with crisis there is a constant mean date at which the crisis occurs for all age-periods. It is found that the variation of this mean date in any group of statistics is always within three times the probable error, and consequently of no significance; that, in fact, at all age periods—no matter what alteration of the tissues may have been produced—there is, if recovery takes place, the same reaction at the same time. Further, the mean date at which death occurs is likewise almost constant. The change which takes place from youth to age in the tissues which renders persons of higher age more easy victims to zymotic disease is, therefore, a greater inability to produce certain bodies at certain times, rather than a want of resistive power in the tissues themselves. It may be seen from the tables this holds for typhus fever, pneumonia, and relapsing fever. The figures given for typhus are those of Dr. Russell. The figures for relapsing fever are those given by Dr. Tennent, while those of lobar pneumonia are based on the records of Belvidere for the last six years; they show essentially the same features (Tables VIII. A, B, C).

TABLE VII.—Table showing the dates of ending of various acute diseases.

	Numbers having crisis on each day from Onset.					Number of Cases of Measles on each day at which the temperature is first			Number of cases of Small-pox having first bath on each day after Onset.‡	
Day of Crisis.	Typhus.*	Typhus.†	Relapsing Fever.*	Pneumonia.	Day of Illness.	101° F.	100° F.	99° F.	Days.	Cases.
1	...	...	...	...	1	...	...	...	4-5	2
2	...	...	...	...	2	...	...	...	6-7	13
3	...	...	1	...	3	3	...	...	8-9	40
4	...	...	9	...	4	5	5	3	10-11	131
5	...	...	20	2	5	9	8	2	12-13	192
6	...	...	46	8	6	18	12	8	14-15	152
7	1	1	14	3	7	13	18	10	16-17	99
8	2	...	7	10	8	2	5	14	18-19	73
9	8	8	3	3	9	5	3	7	20-21	40
10	27	29	...	3	10	2	5	5	22-23	24
11	31	45	...	4	11	...	1	4	24-25	13
12	65	65	...	2	12	1	...	1	26-27	17
13	123	71	...	3	13	...	...	1	28-29	10
14	119	66	...	3	14	...	1	1	30-31	6
15	77	24	...	3	15	...	...	...	32-33	4
16	29	4	...	2	16	...	...	2	34-35	6
17	11	1	...	3	...	...	...	...	36-37	2
18	4	...	...	1	...	..	...	...	38-39	1
19	3	...	...	1	...	...	..	...	40 41	...
20	...	1	...	...	...	...	...	...	42-43	1
21	...	...	...	...	...	...	...	...	..	...
22	...	...	...	...	...	...	...	...	...	...
Total	500	315	100	51	...	50	50	50	...	826

* Murchison's Continued Fevers, p 187, 374. † Glasgow *Medical Journal,* Dr. Russell, 1871.
‡ Karl Pearson, Biometrika, Vol. iv. p. 508.

TABLE VIII. A.—CASES OF TYPHUS FEVER.

DR. RUSSELL'S CASES.*

Age Period, Crisis, and Death.

Day of Crisis or Death.	0-14		15-19		20-30		30-40		40-50		50—	
	Recov.	Death.	R	D	R	D	R	D	R	D	R	D
7	...	..	...	...	...	...	...	...	...	I	...	I
8	...	...	...	...	...	...	...	I	...	...	...	2
9	3	...	2	...	2	...	...	2	...	I	I	3
10	3	I	7	I	7	...	7	2	4	5	I	3
11	3	...	16	2	11	6	3	2	11	I	I	I
12	7	I	12	...	23	I	15	2	4	5	4	2
13	7	...	23	2	19	—	13	I	6	2	3	2
14	2	...	11	I	21	...	17	5	7	2	8	4
15	5	...	7	2	7	4	2	3	3	4	...	I
16	...	...	..	2	2	4	...	2	I	2	I	...
17	..	...	I	I	...	2	...	I	...	I	...	...
18	...	...	...	I	...	2	...	3	...	I	...	2
19	...	...	...	..	...	...	...	...	...	I	...	...
20	...	...	...	...	...	I	...	...	I	...	...	...
21	...	...	..	I	...	I	...	I	...	2	...	...
21-	...	...	...	2	..	5	..	..	...	I	...	I
Total - -	30	2	79	15	92	26	57	25	37	29	19	22
Mean Day Recoveries	12·2	...	12·4	...	12·6	...	12·6	...	12·5	...	12·9	...
Deaths . .	...	11	...	15·6	...	16·2	...	13·7	...	13·8	...	12·2
Mean Day of Death of those under 20 days	...	11	...	14·1 σ=·7	...	14·3 σ=59	...	13·5 σ=40	...	13·0	...	11·8

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* *Glasgow Med. Journal*, 1871.

TABLE VIII. B.—Table showing the duration of the Pyrexial Period in cases of Relapsing Fever.*

Age.	No. of Males.	Mean Duration of Attack in Days.	No of Females.	Mean Duration of Attack in Days.
0-9	16	6·28	23	6·20
10 19	63	7·00	69	6·49
20-29	32	6·70	38	6·58
30-39	19	6·66	29	7·52
40-49	19	7·08	20	7·00
50-59	7	7·50	7	7·00
60-	6	7·16	4	7·00

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* Tennent, *Glasgow Med. Journ.*, 1871, p. 385.

The character of the attack may, however, be measured in other ways, and the relation of the character of the attack to the capacity for acquiring immunity further investigated. One measure suggested at once is the date on which patients suffering from a fever are first stimulated. Dr. Russell's statistics are here of great value. The capacity for acquiring immunity steadily diminishes with age,

TABLE VIII. C.—CASES OF PNEUMONIA TREATED IN BELVIDERE FEVER HOSPITAL, 1901 1906.

Age Periods.

Day of Crisis or Death.	0-10		10 20		20-40		40-	
	R	D	R	D	R	D	R	D
5	1	..	...	...	1	...	...	...
6	4	...	2	...	1	1	1	...
7	...	...	2	...	1	1	...	1
8	3	1	2	...	1	..	...	...
9	...	...	5	...	2	...	3	1
10	1	...	...	1	2	...	...	1
11	...	...	1	1	2	...	...	1
12	...	...	1	1	3	2	...	1
13	..	...	2	...	...	...	...	...
14	1	1	2	...	...	...	...	...
15	...	...	3	...	...	...	...	...
16	...	...	2	..	1	1	...	...
17	2	.	...	..	...	...	..	...
18	...	...	...	1	...	..	2	...
19	...	1	...	...	1	1	...	..
20	1	...	...	...	...	1	..	...
21	...	...	1	...	...	...	...	...
22	...	..	...	...	...	...	...	...
23	...	...	...	..	...	...	...	...
24	...	..	...	...	...	...	1	...
Total . .	13	3	23	4	15	7	7	5
Mean Recoveries	10 0	...	11·3	..	10·4	...	13·3	...
.			20	0-20	upw	ards		
Mean day of death	..	13·1	...	...	...	11·7	...	...

and yet, as will be seen by a reference to Table VIII. D, the date at which stimulant was found to be necessary is singularly constant, showing again that it is not lack of tissue resistance in old persons but lack of some other capacity which determines the issue of the disease.

Again the mean temperature of an attack of disease may be taken as a measure of its severity. A table (Table VIII. E) showing the figures for pneumonia has been constructed according as the mean temperature during the attack was below or above 103 F. The numbers are not very large, and though there is some slight difference shown in the dates of crisis and death it is not beyond what might be expected considering the number of cases. There is thus little difference shown in the results whether severity is measured by date of crisis, necessity of stimulant, or height of the fever.

TABLE VIII. D.—CASES OF TYPHUS FEVER.

Age Period. Day on which first stimulated.

Day on which first stimulated.	0-14		15-19		20-30		30-40		40-50		50—	
	Recov.	Death.	R	D	R	D	R	D	R	D	R	D
5	2	...	1	1	...	...	...	...	1	..	...	1
6	2	...	...	...	...	...	3	1	1	2	1	4
7	3	...	6	2	8	1	4	4	2	2	1	2
8	7	...	17	3	7	6	10	5	3	7	4	4
9	8	...	18	4	19	5	11	4	9	5	4	4
10	4	2	14	2	21	7	13	4	9	6	5	4
11	6	...	7	1	16	1	8	3	1	2	3	1
12	2	...	5	1	9	4	10	2	1	2	...	1
13	6	...	2	1	3	...	3	...	5	...	2	...
14	3	...	4	...	3	...	...	1	1	2	...	...
15	1	...	2	...	...	...	1	...	1	...	...	...
16	...	...	...	...	1	...	...	1	1	...	...	1
17	...	...	1	...	1	1	...	...	...	...	...	...
18	...	...	...	...	...	...	...	...	...	...	...	...
19	...	...	...	...	...	...	...	...	...	...	...	...
20	...	...		...	...	...	...	...	..	...	...	...
21	...	...	1	...	...	1	...	...	...	1	...	...
Total - -	44	2	78	15	88	26	63	25	35	29	20	22
Mean Day of Stimulation	9·9	...	9·8	...	10·2	...	9·8	...	10·1	...	11·8	...
Recoveries .	9·9	...	19·8	...	10·2	...	9·8	...	10·1	...	11·8	...
Deaths - -	...	10·0		9·0	...	10·3	...	9·5	...	9·8	...	9·5

It is more difficult to obtain figures for other diseases which end by lysis. However, some figures were recently taken out with regard to smallpox for a different purpose. The date of the first bath was chosen as representing the end of the disease, and the cases showing an abundant or confluent eruption selected for comparison. A complication arises here as the presence of boils frequently delays the baths, and the larger the surface involved in the smallpox eruption the greater the likelihood of this secondary infection. A series of means has therefore been calculated representing the duration of the illness in all cases ending up to each definite date, and it will be seen that again there is a singular constancy in these means whether the cases be mild or severe, with the exception that there is a greater tail of septic cases among those with a confluent as compared with those with an abundant eruption.

Table VIII. e.—Cases of Pneumonia Treated in Belvidere Hospital, 1901-1906.

Average Temperature.

Day of Crisis or Death.	< 103° F.		> 103° F.	
5	...	...	2	...
6	2	1	6	...
7	1	2	1	...
8	1	...	3	1
9	7	...	3	1
10	1	..	2	2
11	2	1	1	1
12	2	3	2	1
13	1	...	1	...
14	1	...	2	1
15	3	...	...	...
16	3	1	...	...
17	1	...	1	...
18	1	..	1	1
19	1	2	...	...
20	...	...	1	1
21	...	...	1	...
22	...	...	...	...
23	...	...	..	...
24	1	...	...	...
Total	28	10	27	9
Mean, Recoveries .	12·3	...	10·2	...
Mean, Deaths .	--	12·1	...	12·4

The general conclusions which are to be drawn from this series of facts is that for any given disease there is little difference in the method by which immunity is produced, or in the period at which the curative properties of the body come into action, even although the ability of the organism to produce the necessary anti-bodies varies immensely. Thus, between the ages of 15 and

20 the mortality from typhus fever is in Dr Russell's cases (Table VIII.A) about 16 per cent., and in those above 50 years of age over 50 per cent., yet the mean date of crisis is identical, a phenomenon only to be explained on some such basis as this. Nor does the poison of the fever apparently act in a more virulent fashion on older than on younger persons in the sense of producing symptoms of cardiac failure earlier or later. The date on which stimulation was found to be necessary (Table VIII. D) is practically constant from youth to age among those patients who required it, nor is there much evidence that the symptoms of profound poisoning developed much earlier in fatal cases than in the recoveries, the fatal issue being in general apparently due to an inability to produce the necessary protecting substances on the part of the patient rather than to any special virulence of the

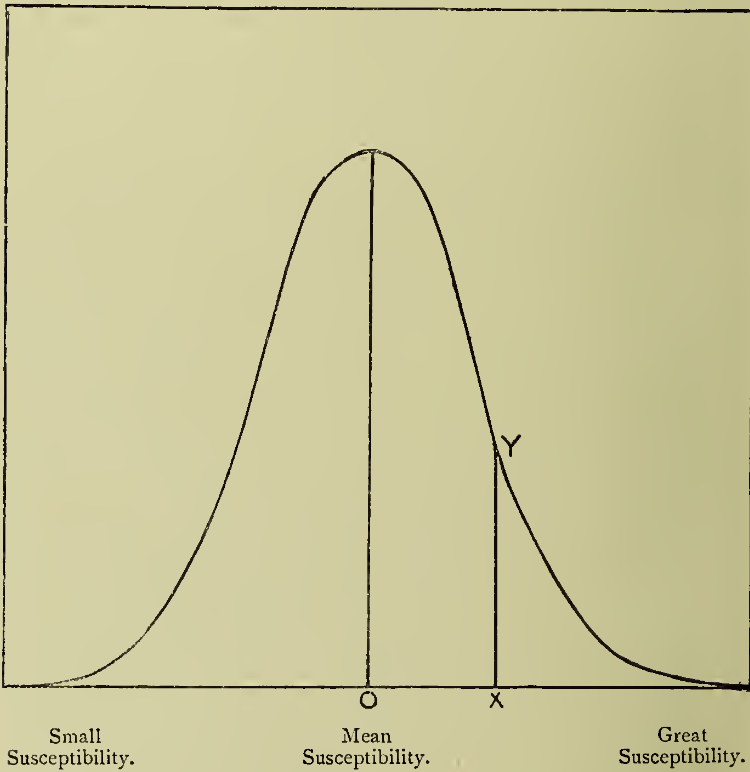
TABLE IX.—Table showing Number of cases of Smallpox in Vaccinated Persons having the first bath on each day after onset of disease, with the corresponding Means.

Day of First Bath.	Eruption.		Mean Duration of all Cases up to the respective day.	
	Abundant.	Confluent.	Abundant.	Confluent.
4	1	1	...	...
5	2	...	...	...
6	...	...	...	..
7	7	1	...	..
8	15	5	...	...
9	18	10	...	...
10	24	9	...	...
11	24	8	...	...
12	27	14	9·8	10·1
13	22	5	...	...
14	20	8	10·8	10·9
15	12	7	...	...
16	6	10	11·4	11·9
17	8	6	...	..
18	3	4	11·8	12·7
19	3	2	...	...
20-25	11	9	...	...
25-30	4	8	..	..
30 40	2	4	...	..
40-50	...	Total,	13·3	15·3
50-60	...	...	...	...

organism infecting those cases which end in death. In support of this it is to be noted that the mean day of death (Table VIII. A) is higher than the mean day of crisis, and even when those cases who died after 20 days of illness are excluded on the ground that some complication probably caused the fatal issue this is yet more marked, another proof that the fatal issue is due to the cause stated and not to less resistance of the tissues. The same facts are also true for pneumonia (Table VIII. C). For typhus fever there is some evidence that among those from 15-30 years of age death takes place at a slightly later period than among those older, and in this case the greater resistance of the tissues in younger persons may easily be the cause of a more protracted struggle against the toxines of the infecting organism, a fight however, useless on account of the inability of the patient to produce the necessary protecting substances.

It has been seen that the incubation period varies continuously from a short to a long one, having a maximum in between with the distribution on either side of this maximum in many cases not far from symmetrical. In the same way the length of a disease where it can be easily measured has been seen to fulfil the same conditions. This measurement is most easily made in the case of disease ending by crisis, but as has been seen in the table is equally true of such diseases as measles and smallpox. It affords one means of measuring the severity of an attack.

The general severity of typhus fever has been measured in two ways in the case of Dr Russell's statistics—one, the date of the crisis, the other the date on which the stimulation was begun. As has been seen the distribution as regards severity afforded by these two methods is essentially the same. There is a mean severity on either side of which the cases tend to group themselves, and the same is true with regard to the deaths. This is an important point as showing the independence of natural immunity and the capacity for acquiring immunity, and it is a general phenomenon throughout disease. It was this fact which made it clear to me first that the processes of natural immunity must be largely different from those displayed in acquiring immunity. An example of this based on some figures given by me was published by Prof. Pearson in *Biometrika*, Vol. IV. p. 508, in a paper criticising another paper in the same number by Dr T. M. Turner in which the opinion was expressed that the mildest cases of the disease should be the most common. If natural immunity depended on the same range of factors as the acquirement of immunity then as of the whole population attacked by an epidemic the great majority escape, it follows that the number of mild cases should be in excess of the number of severer, that is to say there should be a continual increase in number of those infected by the fever as the cases are graded from severe to mild. A reference to the diagram will illustrate this point.



In this diagram the whole population is grouped according to its susceptibility in the general form which such distributions are observed to take, namely, that a mean susceptibility is commonest and that higher and lower susceptibilities become less and less frequent the further they depart from the mean. At the one end of the curve the ordinates represent the number of very susceptible persons, at the other of very insusceptible. If susceptibility be the criterion for infection it follows that an ordinate in some such position as XY will represent the dividing line between those attacked and those escaping, the position of the ordinate on the susceptible side of the mean being determined by the fact that the great majority of the general population escape infection. The ordinates of the part to the right of XY then represent the numbers of persons with different degrees of severity, if susceptibility has any necessary direct relation to severity of attack, *i.e.*, the ordinate XY representing the ultimate limit of susceptibility which permits infection will represent the number of mild attacks. This, it is obvious, is completely at variance with what has been found earlier in this paper (Table VII.) to be the universal rule, namely, that there is a mean severity of attack on either side of which milder or severer tend to group themselves. This seems to prove that natural immunity and the capacity for acquiring immunity, or in other words the susceptibility to disease and the tendency to severity must depend at least very considerably on different mechanisms.

Note.—All the data here considered refers to diseases acquired by the ordinary processes of nature, and not by artificial methods such as inoculation in the laboratory.